Vascular Endothelial Growth Factor and Social Support in Patients with Ovarian Carcinoma

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BACKGROUND. The modulation of immunologic activities relevant to cancer by behavioral factors, such as stress, depression, and social support, is well documented. However, associations of behavioral factors with cytokines involved in tumor angiogenesis have not been studied. Vascular endothelial growth factor (VEGF) is a key cytokine that is capable of stimulating tumor angiogenesis, and it has been associated with poorer survival in patients with ovarian carcinoma. VEGF is modulated by a variety of behaviorally sensitive factors, including sympathetic activation. This study examined relationships of social support and depressive symptoms with VEGF levels in preoperative patients with ovarian carcinoma.

METHODS. Twenty-four women with ovarian carcinoma and 5 women with benign pelvic masses were recruited at the presurgical clinic visit, received psychosocial surveys, including the Functional Assessment of Cancer Therapy (Quality of Life) survey and the Profile of Mood States, and a blood draw. Serum VEGF levels were assessed by enzyme-linked immunosorbent assay. Analyses controlled for disease stage.

RESULTS. Women with ovarian carcinoma who reported higher levels of social well being had lower levels of VEGF ($P = 0.005$). Greater support from friends and neighbors ($P = 0.005$) and less distance from friends ($P = 0.04$) were facets of social well being that were associated with lower VEGF levels. Individuals who reported greater helplessness ($P = 0.03$) or worthlessness ($P = 0.08$) had higher VEGF levels, but depression as a whole ($P > 0.50$) was not related to VEGF levels.

CONCLUSIONS. Higher levels of social well being were correlated with lower VEGF levels in presurgical patients with ovarian carcinoma. These findings suggest a possible mechanism by which poor social support may be associated with disease progression. Further study of these relations may demonstrate novel pathways relating biobehavioral factors to tumor growth and disease progression. ***Cancer* 2002;95:808–15.** *© 2002 American Cancer Society.*
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Growing evidence has indicated that psychological factors, such as stress, depression, and social support, are able to modulate many of the immunologic activities relevant to patients with malignant disease. There is substantial evidence demonstrating consistent associations between chronic stress, depressed mood, and decrements in facets of cellular immunity, including natural killer cell activity and alterations in production of cytokines, such as interleukin-2 (IL-2), interferon γ, and IL-6.[1–11] Disruptions in interpersonal relations, loneliness, and social isolation generally have been related to immunocompromise, whereas higher levels of social support have been associated with less compromise in measures of cellular immunity.[12–15]

Effects of behavioral factors on immunologic activities relevant to patients with malignant disease are mediated in part by the sympathetic nervous system,[16] by the hypothalamic-pituitary-adrenal axis,[17,18] and by a variety of hormones and peptides.[19,20] Biobehavioral-immune research in patients with malignant disease has focused largely on the effects of behavioral factors on immune cells, cytokines, and hormones that modulate cellular immunity.[1,21–24] These factors are related to tumor control through mechanisms such as cell lysis or activation of immune cells to a lytic state. Although modulation of cytokines by biobehavioral factors has been well documented,[2,5,6,8,10,11] there are no published data examining relationships of biobehavioral factors with cytokines involved in tumor angiogenesis, a critical mechanism in the development and growth of malignant disease.

The growth of most solid tumors and their metastatic spread is dependent in part on angiogenesis. Most primary solid tumors go through a prolonged state of avascular growth in which the maximum size attainable is 1–2 mm in diameter.[25] When angiogenesis is switched on, surrounding blood vessels are recruited for tumor perfusion, resulting in tumor growth and metastases.[25,26] Angiogenesis is tightly controlled by a number of positive and negative factors.[25] Of the numerous promoters of angiogenesis that have been identified, one of the most potent appears to be vascular endothelial growth factor (VEGF), a homodimeric, 32–42 kDa, heparin-binding glycoprotein.[27] VEGF is a multifunctional cytokine and is produced by a variety of cells, including tumor cells, endothelial cells, tumor-associated inflammatory cells, neutrophils, platelets, and mononuclear cells.[28–31] VEGF stimulates endothelial cells in microvessels to proliferate, migrate, and alter their pattern of gene expression. It also makes cells hyperpermeable, resulting in conditions that favor angiogenesis in the extracellular matrix.[32] VEGF may be an important prognostic marker in patients with ovarian carcinoma, because higher VEGF levels are associated with metastatic disease[33] and poorer survival.[34,35] VEGF is regulated by a number of cytokines, including IL-6,[36]; hormones; and growth factors,[37,38] including gonadatropic, steroid, and other hormones.[39] VEGF also is induced by norepinephrine[40,41] through β-adrenoreceptors[42] and is inhibited by dopamine.[43] We previously reported that patients with gynecologic malignancies who reported high levels of social support utilization preoperatively had lower levels of plasma IL-6.[44] Patients with higher levels of social support utilization also had better 1-year disease outcomes, controlling for extent of disease and functional status at baseline.[44] Furthermore, IL-6 increased with both acute and chronic stress[11,45–47] and with depression[48] and decreased after treatment of depression.[49] This led us to hypothesize that VEGF, as a cytokine induced by IL-6, also may be related to biobehavioral factors.

Social support is frequently defined as the degree of one's perceived participation in satisfactory social relations.[50] There is a substantial body of research relating higher levels of social support to lower morbidity and mortality from a variety of diseases.[51–53] It has been proposed that social support has direct benefits on health (in the absence of stress) as well as stress-buffering effects,[50] and there is empiric support for both of these models.[14] According to the stress-buffering model, social support acts by moderating the detrimental physiologic effects of the stress response. For example, a patient with good social support will perceive potentially threatening events as less stressful because of the added resources that support provides for dealing with the stressor.[50] The net result will be lower stress-related arousal and, thus, less allostatic load, or less stress-related *wear and tear* on the organism, resulting in less compromise to immunity and other physiologic systems.[14,54]

Because it has been shown that VEGF has prognostic implications in ovarian carcinoma,[35] this investigation focused on patients with ovarian carcinoma. It was hypothesized that psychosocial factors, such as social support, would be related to lower levels of VEGF and that depressed mood or a history of depression would be related to higher preoperative VEGF levels in patients with ovarian carcinoma.

MATERIALS AND METHODS

Patients

Inclusion criteria

Women age $\geq$ 18 years with a pelvic mass suggestive of ovarian carcinoma were eligible for the study. Patients with previous cancer at another site, previous treatment for the current carcinoma, ovarian germ cell cancer, or a primary tumor of another organ were excluded.

Sample characteristics

Twenty-nine women were recruited. There were 24 women with ovarian carcinoma: Five women with Stage I–II disease and 19 women with advanced stage (Stage III or IV) disease. Twenty-two patients had high-grade disease (Grade 2 or 3). Five women with pelvic masses that turned out to be benign ovarian tumors were included in the study as a comparison group for levels of VEGF.

Measures

Quality of life

The Functional Assessment of Cancer Therapy (FACT-G) is a 28-item scale that measures quality of

life (QOL) in patients with malignant disease.[55] This instrument was selected because of its previous validation and extensive use among patients with malignant disease. Subscales assessing physical, functional, emotional, and social well being and satisfaction with treatment providers have been supported by factor analysis. Patients rate statements about their well being by indicating how true each statement has been during the previous 7 days from 0 (*not at all*) to 4 (*very much*), with higher scores indicating better QOL. The discriminant validity of the FACT has been demonstrated, in that it is able to distinguish between patients of different disease stage and performance status and between inpatients and outpatients receiving treatment.[55] Because of previous findings of a correlation between a social support factor and IL-6,[44] the subscale of social well being was the subscale of interest in this measure.

Distress

The Profile of Mood States (POMS) scale lists 65 adjectives to which patients respond according to their mood over the past week.[56] These are rated on a 5-point scale from 0 (*not at all*) to 4 (*extremely*), and scores are summed to create each subscale. Six factors have been identified to describe scale items: anxiety, depression, anger, vigor, fatigue, and confusion. The POMS has shown good external validity and has been used previously to assess distress in patients with gynecologic malignancies and with other types of malignant disease.[57,58] The depression subscale was the scale of greatest interest in this study. In addition, patients were asked whether they had ever received psychiatric treatment for depression or anxiety.

VEGF

Detection of VEGF present in plasma was performed by an enzyme-linked immunosorbent assay using a standard kit (VEGF Quantkine Kit; R&D Diagnostics, Minneapolis, MN), with measurements performed according to the manufacturer's instructions, and the results were interpolated from the standard reference curve provided with the kit. The minimum detectable level of VEGF was < 5.0 pg/mL.

Demographics

Demographic information, such as age, marital status, education, income, and living arrangements, was collected. Responses were given in multiple-choice format according to the level of data (e.g., education less than high school, high school, some college, trade school, college graduate, or postgraduate education).

Procedure

All data were collected in compliance with the University of Iowa Review Board, and informed consent was obtained from all participants. Patients were recruited at their initial clinic visit, which was generally between 2 days and 14 days before surgery. They completed psychosocial questionnaires and gave a 10-mL. sample of peripheral venous blood in Vacutainer tubes (Becton Dickinson Company, Rutherford, NJ) prior to surgery. Eligibility for study participation was confirmed by pathologic examination at the time of surgery.

Statistical Analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (version 8.0 for PC; SPSS, Chicago, IL). All distributions were examined for outliers and nonnormality. A square-root transformation was used to normalize VEGF data, which were skewed positively. Values for VEGF given in the text and figures are conversions from the transformed values to raw values. One-way analyses of variance (ANOVAs) were used to examine whether VEGF levels varied based on stage or grade of disease or according to demographic characteristics. ANOVAs also were used to compare the VEGF levels of patients who had ovarian carcinoma with the VEGF levels of women with benign tumors and to compare the social well being of patients with high and low levels of VEGF. Hierarchical regression analyses were used to examine the correlation of FACT subscales, the POMS Depression Scale, and previous diagnoses of depression or anxiety with VEGF levels. To provide greater information regarding facets of social well being and depression that were associated with VEGF, relationships of specific scale items and VEGF were modeled. As a conservative measure, disease stage was used as a covariate in all regression models and in ANOVAs that were conducted within the patient group.

RESULTS

Participant Characteristics

The mean age of patients with ovarian carcinoma was 62.17 years ($\pm$ standard deviation [SD], 12.10 years; range, 38–81 years), and all patients were Caucasian. The median education was completion of high school, and the median annual income was \$10,000–\$20,000. Patients with ovarian carcinoma had a mean $\pm$ SD preoperative VEGF level of 315.41 $\pm$ 92.54 pg/mL (range, 30–1785 pg/mL). There were no significant differences in VEGF levels based on stage or grade of disease (all $P > 0.30$). Participants in the control group with benign pelvic masses had a mean $\pm$ SD preop-

TABLE 1
Regression Models of Vascular Endothelial Growth Factor Levels as Predicted by Social Well Being in Patients with Ovarian Carcinoma[a]

Predictor variable	R	ΔR^2	β	F (of ΔR^2)[b]
Covariate: Disease stage	0.23	0.05	− 0.12	1.26
Social well being	0.59	0.30	−0.56[c]	9.67[c]

[a] The outcome variable was the level of vascular endothelial growth factor. ΔR^2 refers to the percentage of variance in the dependent variable contributed by the predictor variable in each model. The β weight refers to the strength of association of an individual predictor with the outcome variable, with all other predictors in the model.
[b] Significance of model $F(2.21) = 5.71$ ($P = 0.01$).
[c] $P < 0.01$.

erative VEGF level of 38.87 ± 3.88 pg/mL (range, 19–90 pg/mL). Because the mean age of these women with benign pelvic masses was slightly younger than that of the patients with ovarian carcinoma (51.40 ± 14.17 years; range, 36–70 years; $P = 0.09$), age was used as a covariate when comparing VEGF levels between the two groups. Chi-square tests indicated that there were no differences between the patient group and the control group in any demographic variable (all $P > 0.15$). Patients with ovarian carcinoma had significantly higher levels of VEGF compared with women who had benign masses ($P = 0.014$). Among the patients with ovarian carcinoma, 33.3% had VEGF levels > 380 pg/mL, a value that was associated previously with poorer survival.[35] There were no associations of marital status, living arrangements, education, or income with VEGF levels (all $P > 0.10$).

Hierarchic regression analyses, controlling for disease stage at diagnosis (which was not significant), indicated that greater social well being was significantly related to lower levels of VEGF ($\beta = 0.56$; $P = 0.005$). The β weight refers to the strength of association of an individual predictor and the outcome variable with all other predictors in the model (see Table 1, Fig. 1). To provide greater information regarding the facets of social well being that were associated with VEGF, parallel regression models were constructed examining associations between specific items on the social well being scale and VEGF, using disease stage as a covariate. Patients who reported a greater distance from friends had significantly higher levels of VEGF ($\beta = 0.42$; $P < 0.05$), whereas patients who reported greater support from friends and neighbors ($\beta = -0.58$; $P = 0.004$) and support from family ($\beta = -0.42$; $P < 0.05$) had lower levels of VEGF. No other FACT subscales were related to VEGF levels (all P values > 0.20).

In addition, patients were divided into those with VEGF > 380 pg/mL ($n = 8$ patients) and those with VEGF < 380 ng/mL ($n = 16$ patients) because VEGF levels > 380 pg/mL have previously been noted as a prognostic value for poor survival. Patients with VEGF levels below this cut-off value reported significantly higher levels of social well-being (mean ± S.D.: 25.23 ± 3.01 pg/mL) compared with patients with VEGF levels above this cut-off value (20.27 ± 5.35 pg/mL; $P = 0.008$). These findings were independent of disease stage, which was used as a covariate.

The POMS Depression Scale, as a whole, was not significantly related to VEGF levels ($P > 0.80$). However, because this scale includes both affective items (e.g., *blue*) and cognitive items (e.g., *helpless),* we examined specific items related to more cognitive aspects of depression, such as *helpless* and *worthless.* Higher levels of helplessness ($\beta = 0.43$; $P = 0.03$) were associated significantly with higher VEGF levels. There was a trend toward an association between higher levels of feeling worthless and higher VEGF levels ($\beta = 0.36$; $P = 0.08$). These two aspects of depressive symptoms are associated more with self-concept than with mood. In addition, patients who reported a prior history of treatment for depression or anxiety had a trend toward higher VEGF levels ($\beta = 0.41$; $P = 0.06$).

DISCUSSION

This study examined relationships of social well being and depressive symptoms with serum VEGF levels, a marker of angiogenesis that is indicative of a poor prognosis in patients with ovarian carcinoma. This patient population in the current study was representative of patients with ovarian carcinoma, because 75% of them had Stage III or IV disease at the time of diagnosis. Preoperative patients with ovarian carcinoma who reported higher levels of social well being had lower VEGF levels, whereas patients who reported greater helplessness had higher VEGF levels. Those individuals with levels of VEGF above cut-off values associated with poor survival had relatively low levels of perceived social well being. Although a measure of depressive symptoms as a whole was not associated with VEGF, there was a trend toward an association of a previous psychiatric history and a sense of worthlessness with higher levels of VEGF. The association between VEGF and social well being was sufficiently robust for a significant correlation to be detected even in this small sample.

The observed correlation between social support and VEGF is consistent with our previous observations of an association between higher levels of social support utilization and lower IL-6 levels in patients with gynecologic carcinoma.[44] In the current data, living with a spouse or children compared with living alone and the presence or absence of a marital relationship

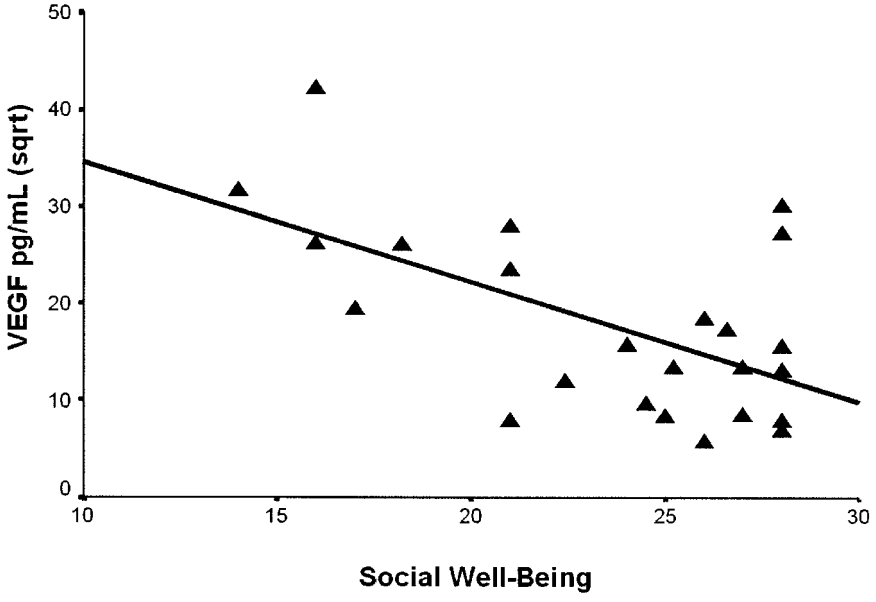

FIGURE 1. The relationship between social well being and vascular endothelial growth factor (VEGF) levels (in pg/mL; square-root transformation) in presurgical patients with ovarian carcinoma. Social well being was a significant predictor of VEGF levels β [the strength of association of an individual predictor and the outcome variable with all other predictors in the model] = 0.57; $P = 0.005$). Higher levels of social well being were associated with lower VEGF levels, and the entire model was significant ($P = 0.01$).

were not related to levels of VEGF. Rather, it was the perception of emotional support and ability to count on others that was related to lower VEGF levels. This is consistent with other literature suggesting that it is not only the presence of others but the quality of relationships with others that appears to be related to physiologic parameters.[14] Social support has been shown to modulates the immune response to acute laboratory stressors[59] as well as chronic stressors,[60] and social support has been associated with lower tonic levels of neuroendocrine stress hormones, such as epinephrine, norepinephrine, and cortisol.[61–64] Stress reduction also has been associated with the reduction of levels of these hormones.[65,66] Because VEGF can be induced by norepinephrine[40,41] through β-adrenoreceptors,[42] potential physiologic mediation of a correlation between social support factors and VEGF levels may include lowered activation of sympathetic pathways.

This is the first report noting an association between a psychosocial factor and a cytokine involved in tumor angiogenesis among patients with malignant disease: A Medline search of the last 5 years did not reveal any such observations. These findings suggest a novel mechanism by which biobehavioral factors may be associated with the progression of ovarian carcinoma. Findings of a relationship between a social support factor and VEGF are consistent with a biobehavioral model of malignant disease that proposes multifactorial pathways by which psychologic processes and health behaviors interact with biologic processes that, in turn, influence physiology and tumor resistance.[67] Understanding the mechanisms of such interactions and the type and magnitude of their potential effects is an important goal of future research.

Limitations

These findings should be viewed in light of a number of caveats. Whereas the current data support a relationship between a behavioral variable and a cytokine that is important to the progression of ovarian carcinoma, because of the cross-sectional nature of the data, causal inferences from this data are limited and should be explored in future prospective work. It also should be noted that, although social support was assessed using a QOL instrument that had been validated on patients with malignant disease, this instrument measures only limited aspects of social support; thus, future research replicating these findings with a more extensive measure of social support is warranted.

Because the constructs of *worthlessness* and *helplessness* were measured by single item scores rather than by full scales measuring these constructs, the findings regarding these aspects of depression should be taken as preliminary and should be replicated in future work with more extensive measurement of these constructs. In addition, because a past history of depression or anxiety was related marginally to VEGF, a more comprehensive measurement of depression, anxiety, and past mental health history is warranted in future work. The magnitude of association between aspects of depression and VEGF appears to be smaller than that of VEGF and social well being; thus, constructs related to depression should be explored in a larger sample with greater power before concluding

that there is no association between VEGF and depressive symptoms.

It should be noted that the range and standard deviation for VEGF are relatively large. Even so, there were relatively few patients with ovarian carcinoma (n = 5 women) who had levels of VEGF that fell within 1 standard deviation of the mean of the benign comparison group. It is interesting to note that all of these patients had Stage III disease, and all reported relatively high levels of social well being. Future studies examining other characteristics of these patients with low VEGF levels are indicated. In addition, examination of a larger comparison group in future work also is indicated.

Although it is believed that VEGF in peripheral blood is a good indicator of survival in patients with ovarian carcinoma, it is not known to what degree peripheral VEGF levels reflect secretion of VEGF at the tumor site. Determining correlations of peripheral and tumor VEGF and whether there are associations of behavioral factors with VEGF at the tumor site is therefore an important goal of future work.

CONCLUSIONS

Despite these caveats, the current findings are unique and point to the possibility of novel pathways between biobehavioral factors and tumor angiogenesis that may contribute to disease progression in patients with ovarian carcinoma.

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